attn: Fr. Hollak
02111577560

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN APPLICATION OF	
WOLFGANG EBENBECK ET AL	GROUP NO.: 1626
SERIAL NO.: 10/751,623	CONFIRMATION NO.: 2430
FILED: JANUARY 5, 2004	EXAMINER: REBECCA L. ANDERSON
TITLE: FLUORINATING REAGENTS AND THEIR PREPARATION	

DECLARATION UNDER 37 CFR 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Dr. Wolfgang Ebenbeck declare as follows:

1. I studied chemistry at the University of Regensburg and obtained a Ph.D. in 1999. Since 2004 I have been employed by LANXESS Deutschland in Leverkusen as a Head of Fluorine Chemistry.

2. I am familiar with the subject matter of the above-identified United States patent application.

3. I performed or supervised the following experiments:

Example A (according to the present invention)

Reaction of (2S-trans)-N-(tert-Butoxycarbonyl)-4-hydroxyproline benzyl ester with the fluorination reagent 1,1-difluoro-N,N-2,2-tetramethyl-1-propanamine from example 1 of the Application as filed:

Under a protective gas atmosphere, a solution of 10,0 g (31.1 mmol) (2S-trans)-N-(tert-Butoxycarbonyl)-4-hydroxyproline benzyl ester dissolved in 25 ml CH_2Cl_2 is dropwise added to a stirred solution of 7.5 g (32.7 mmol) of 1,1-difluoro-N,N-2,2-tetramethyl-1-propanamin in 25 ml CH_2Cl_2 at -15°C. After the reaction mixture is allowed to warm to 0°C, stirring is continued for another 4 h at reflux and conversion rate is monitored by GC. The reaction is

quenched by addition of 80 ml of aqueous $NaHCO_3$-solution, the aqueous phase is separated and extracted by addition of 50 ml CH_2Cl_2. The combined organic phases are dried over $MgSO_4$ and the solvent is evaporated to yield (2S, 4S)-N-(tert-butoxycarbonyl)-4-fluoroproline benzyl ester. After hydrogenation (2 atm) at 20°C for 18 h in MeOH in the presence Pd/C (2S, 4S)-N-(tert-Butoxycarbonyl)-4-fluoroproline is obtained and diastereomeric excess was determined by HPLC.

de = 98%

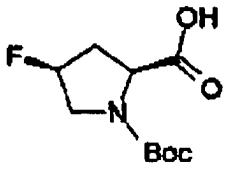
Example B (comparative example)

Reaction of (2S-trans)-N-(tert-Butoxycarbonyl)-4-hydroxyproline benzyl ester with the fluorination reagent 1,1-difluoromethyl-N,N-dimethylamine. Reagent 1,1-difluoromethyl-N,N-dimethylamine corresponding to the '062 reference:

Under a protective gas atmosphere, a solution of 6,60 g (21.2 mmol) (2S-trans)-N-(tert-Butoxycarbonyl)-4-hydroxyproline benzyl ester dissolved in 15 ml CH_2Cl_2 is dropwise added to a stirred solution of 2.1 g (22.2 mmol) of 1,1-difluoromethyl-N,N-dimethylamine in 15 ml CH_2Cl_2 at -15°C. After the reaction mixture is allowed to warm to 0°C, stirring is continued for another 3,5 h at reflux and conversion rate is monitored by GC. The reaction is quenched by addition of 50 ml of aqueous $NaHCO_3$-solution, the aqueous phase is separated and extracted by addition of 30 ml CH_2Cl_2. The combined organic phases are dried over $MgSO_4$ and the solvent is evaporated and (2S-trans)-N-(tert-Butoxycarbonyl)-4-fluoroproline benzyl ester is isolated. Hydrogenation (2 atm) at 20°C for 16 h in MeOH in the presence Pd/C yielded (2S, 4S)-N-(tert-butoxycarbonyl)-4-fluoroproline.

de = 82%

(2S, 4S)-N-(tert-Butoxycarbonyl)-4-fluoroproline:



^{1}H-NMR: 12.5 ppm (br s, 1H, -COO*H*); 5.2 ppm (d, 1H, -C*H*F-); 4.3 ppm (t, 1H, -C*H*CO_2H), 3.5 ppm (m, 2H, -CH_2-); 2.2-2.8ppm (2 m, 2H, -CH_2-), 1.3-1.4 ppm (2 s, 9H, tButyl)

4. CONCLUSIONS

In the foregoing Examples, 1,1-difluoromethyl-N,N-dimethylamine, reagent according to the present invention and 1,1-difluoromethyl-N,N-dimethylamine, reagent according to the '062 reference, were both employed as fluorination reagents in the fluorination of (2S-trans)-N-(tert-Butoxycarbonyl)-4-hydroxyproline benzyl ester. It was surprisingly shown that Example A employing 1,1-difluoro-N,N-2,2-tetramethyl-1-propanamine as the reagent showed, unexpectedly, much higher diastereomeric excess than when 1,1-difluoro-N,N-2,2-tetramethyl-1-propanamine is employed. Therefore, the compound according to the present invention show remarkable improvements in diastereomeric excess when employed as a fluorination reagent over the compound found in the '062 reference.

5. The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Signed at Leverkusen, 27th of March, 2008.

NAME